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INSTITUTE REPORT NO. 461

COMPARISON OF INTRAOSSEOUS AND INTRAVENOUS DELIVERY OF HYPERTONIC SALINE/DEXTRAN (HSD) IN ANESTHETIZED, EUVOLEMIC PIGS

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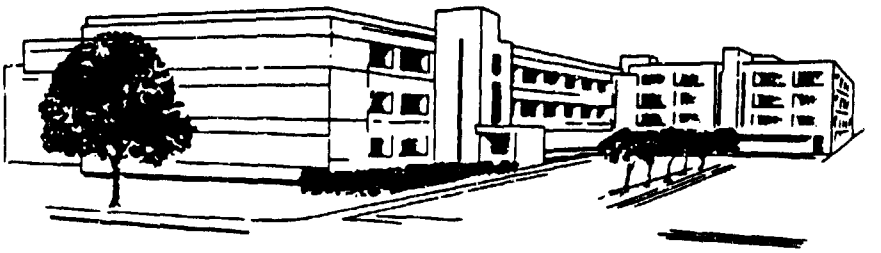
Division of Military Trauma Research

April 1991



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Comparison of Intraosseous and Intravenous Delivery of Hypertonic Saline/Dextran (HSD) in Anesthetized, Euvolemic Pigs, M.A. Dubick et al.

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UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFED	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release Distribution is unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Inst Report No. 461	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Letterman Army Institute of Research 6b. OFFICE SYMBOL (If applicable) SGRD-ULT-M	7a. NAME OF MONITORING ORGANIZATION US Army Medical Research and Development Command
6c. ADDRESS (City, State, and ZIP Code) Division of Military Trauma Research LAIR Presidio of San Francisco, CA 94219-6800	7b. ADDRESS (City, State, and ZIP Code) Ft. Detrick, Frederick, MD 21701
8a. NAME OF FUNDING/SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code)	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 63807A; PROJECT NO. D836; TASK NO. AX; WORK UNIT ACCESSION NO. 087

11. TITLE (Include Security Classification)
Comparison of Intraosseous and Intravenous Delivery of Hypertonic Saline/Dextran (HSD) in Anesthetized, Euvolemic Pigs

12. PERSONAL AUTHOR(S)
M.A. Dubick, J.W. Pfeiffer, C.B. Clifford, D.E. Runyon, G.C. Kramer

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Institute	FROM _____ TO _____	1991 April 1	17

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	(U) intraosseous, hypertonic resuscitation, dextran, pigs (U)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Delivery of fluids and drugs by intraosseous (IO) infusion has seen renewed use in pediatrics and has been proposed for adult use. To evaluate the efficacy of IO infusion of resuscitation fluids in adults, the present study investigates vascular entry cardiodynamic (CD) responses to IO and IV infusion of the small volume resuscitation formulation, 7.5% NaCl/6% Dextran-70 (HSD) in 12 anesthetized, euvolemic pigs. Using a sternal IO access device, 4 ml/kg HSD was infused over 2-6 min; each IO infusion was paired with an IV infusion of equal time. IO and IV HSD infusion produced similar CD effects and increased plasma volume over 20% for the 2 h experimental period. Delivery of Na and dextran was essentially complete within 1 min after infusion and plasma Na and dextran concentrations were comparable over the 2 h period. Histological examination of marrow showed a small, focal hemorrhage as the predominant effect of IO infusion of HSD.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION	
☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	UNCLASSIFIED	
22a. NAME OF RESPONSIBLE INDIVIDUAL Donald G. Corby, COL, MC	22b TELEPHONE (Include Area Code) (415) 561-3600	22c. OFFICE SYMBOL SGRD-ULZ

DD Form 1473, JUN 86 *Previous editions are obsolete.*

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

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Comparison of Intraosseous and Intravenous Delivery of Hypertonic Saline/Dextran (HSD) in Anesthetized, Euvolemic Pigs

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ABSTRACT

Delivery of fluids and drugs by intraosseous (IO) infusion has seen renewed use in pediatrics and has been proposed for adult use. To evaluate the efficacy of IO infusion of resuscitation fluids in adults, the present study investigates vascular entry cardiodynamic (CD) responses to IO and IV infusion of the small volume resuscitation formulation, 7.5% NaCl/6% Dextran-70 (HSD) in 12 anesthetized, euvolemic pigs. Using a sternal IO access device, 4 ml/kg HSD was infused over 2-6 min; each IO infusion was paired with an IV infusion of equal time. IO and IV HSD infusion produced similar CD effects and increased plasma volume over 20% for the 2 h experimental period. Delivery of Na and dextran was essentially complete within 1 min after infusion and plasma Na and dextran concentrations were comparable over the 2 h period. Histological examination of marrow showed a small, focal hemorrhage as the predominant effect of IO infusion of HSD. These data indicate that IO delivery of HSD is as rapid as IV delivery, and may be a viable alternative for emergency resuscitation where vascular access is compromised.

Comparison of Intraosseous and Intravenous Delivery of Hypertonic Saline/Dextran (HSD) in Anesthetized, Euvolemic Pigs -- Dubick et al.

Introduction

In recent years, a number of reviews and reports have re-introduced the use of intraosseous (IO) infusion of fluids and drugs in emergency situations (1-7). The emphasis of IO infusion in these previous studies concerned initial resuscitation and drug delivery in childhood emergencies. It is apparent, however, that IO infusion into red bone marrow could be utilized for rapid vascular access in patients of all ages, under circumstance where securing a peripheral or central intravenous (IV) line is difficult or delayed.

The majority of studies employing IO infusions have used the tibia as the site of infusion (7-12), although the sternum has also been used (11-12). In pediatric patients the proximal tibia is the preferred site for IO access (5). However, in adults the red marrow of long bones is replaced with relatively avascular yellow or fatty marrow. Thus, in adults the sternum or bones of the pelvic girdle are the main sites of red marrow, and have been used for IO infusion (11-12).

In our ongoing investigations into the efficacy of 7.5% NaCl/6% Dextran-70 (HSD) for treatment of hypovolemia, we have begun evaluating sternal infusion of HSD as a viable alternative in field resuscitation. The sternum's large marrow space of uniform geometry is a definite advantage, along with its lying under only a thin layer of skin. Consequently, an IO access device was developed to provide rapid, reliable vascular access through the sternum (13).

In preliminary studies with this device, IO infusion of 200 ml of HSD over 2 to 4 min was used to successfully resuscitate sheep from moderate hemorrhagic shock (14,15). While IO infusion of HSD was rapidly effective in resuscitation from hemorrhagic hypotension (14,15), IO infusion of normal saline (NS) was more slowly effective, as vascular entry of the much larger volume of NS required for resuscitation was impeded by the marrow's naturally high resistance to flow. Encouraged by these preliminary studies with IO delivery of HSD, the present study evaluates the rate of vascular entry of HSD using IO infusion in euvolemic swine and compares with data following IV infusion. Additionally, lungs and sternum were evaluated to detect any significant acute histopathology associated with the IO infusion of HSD.

Materials and Methods

Animals and Treatment

Twelve immature Yorkshire swine (33.7±2.7 kg) were obtained from the colony at the University of California, Davis. Animals were housed individually in an indoor laboratory holding facility with a 12 h light/dark cycle, were maintained at constant temperature and humidity, and were fed commercial chow and water ad libitum.

Animals were fasted 24 hours before surgery. Swine were premedicated with ketamine HCl (~2 mg/kg), xylazine HCl (~2 mg/kg) and atropine (~0.1 mg/kg) and then anesthetized with halothane (1-2%), nitrous oxide 50%, and oxygen for the entire experiment. Pigs were allowed to breathe spontaneously. Catheters were placed in the aorta and vena cava via the carotid artery and jugular vein for infusions and pressure monitoring as needed. To monitor central venous and pulmonary artery pressures and to determine cardiac output, a 7 French Swan Ganz thermal dilution catheter was placed into the pulmonary artery via the internal jugular vein. The femoral artery was catheterized for bleeding and blood sampling. A baseline period of 60 minutes was allowed before beginning each experiment. Pigs remained anesthetized throughout the entire experimental period.

After the baseline period a 4 ml/kg dose of 7.5% NaCl/6% Dextran 70 (HSD; Pharmacia AB, Uppsala, Sweden) was infused into either the manubrium (n=6) or the jugular vein (n=6). Blood samples were taken at 5, 30 and 60 minutes before infusion and at 1, 2, 4, 6, 10, 15, 30, 45, 60, and 120 minutes after the end of the infusion. The times required to infuse HSD IO were noted, and paired with an IV experiment of identical infusion time.

Physiological Measurements

A multichannel monitor continuously recorded arterial pressure, central venous pressure, pulmonary arterial pressure, heart rate and ECG throughout the experiments. Systemic arterial pressure, heart rate, central venous pressure, pulmonary artery and wedge pressure were recorded at 3 baseline time periods and at 1, 2, 4, 10, 15, 30, 60, and 120 minutes after infusion. Cardiac output was

determined by thermodilution at 2, 10, 15, 30, 60 and 120 minutes after infusion. Blood samples taken from the arterial line were used for biochemical analysis and determination of plasma volume.

Biochemical Assays

Total carbohydrate concentrations in plasma were determined by the anthrone reaction (16) following precipitation of serum protein with 10% trichloroacetic acid (TCA). Plasma glucose was determined by an automated glucose-hexokinase enzymatic method performed by the Analytical Chemistry Branch, Letterman Army Institute of Research (LAIR). Plasma dextran concentrations were then estimated by subtracting the glucose concentrations from the concentrations of total carbohydrate.

Assays for sodium, potassium, chloride and protein were also performed by the Analytical Chemistry Branch, LAIR. Plasma sodium and potassium concentrations were determined with a flame photometer (Instrumentation Laboratory, Lexington, MA). Chloride and protein concentrations were determined by a commercial kit (Roche Diagnostic Systems, Nutley, NJ) and the Biuret method, respectively, both adapted for analysis on a Cobas Fara II centrifugal fast analyzer (Roche Analytical Instruments, Belleville, NJ).

Other assays

Plasma volume was determined at baseline using the Evans blue dye dilution method (17). Plasma volume expansion after infusion of HSD was calculated from the baseline plasma volume and the decrease in plasma protein concentration or hematocrit (18).

Histological Evaluation

All animals were examined at necropsy. Tissues were saved in 10% neutral buffered formalin. Lungs were inflated at a pressure of approximately 30 cm water with formalin. A cross section of sternum at the injection site, and liver, kidney, spleen, and heart or any gross lesions were routinely examined by light microscopy. In addition, six sagittal sections of the left inferior lobe of the lung, plus lung sections from any gross pulmonary lesions were examined by light microscopy. All light microscopy was of 4-6 micron thick paraffin sections stained with hematoxylin

and eosin. Any histologic lesions observed were graded on a scale of 1 to 5, where 1= minimal, 2= mild, 3= moderate, 4= marked, and 5= severe. A particular focus of the inspection of lung tissue was evidence for thrombi, fat or bone emboli, necrosis or hemorrhage. Similarly, the sternal sections were examined for decreased cellularity (washout) or hemorrhage.

Statistical Analysis

Data were statistically analyzed by 2-way ANOVA with time and either infusion route or infusion time as the variables (19). Data were also analyzed by co-variate analysis (19) to adjust for differences in infusion time between the two groups. The ANOVA was corrected for repeated measures on the time factor. A $p<0.05$ was taken as the level of significance.

Results

In two of the pigs, the IO infusion of 4 ml/kg HSD into the sternum required 2 min; the remaining pigs required 3, 4, 5, and 6 min each. Therefore, to insure proper matching of infusion times, 4 ml/kg HSD was administered IV to an equal number of pigs in times corresponding to the IO infusion.

Baseline values for mean arterial pressure (MAP) and cardiac output (CO) were similar for all pigs prior to HSD infusion (Figure 1). IO and IV infusion induced an immediate, transient decrease in MAP, typically observed in anesthetizedpigs, that returned to pre-infusion pressure 1 to 4 min after infusion (Figure 1A). No significant differences were observed in MAP between the IO and IV groups throughout the 2 h experimental period.

In pigs infused IO with HSD, CO was increased 18% over baseline values at the end of infusion (independent of the infusion time) and remained about 20% above baseline throughout the experimental period (Figure 1B). CO appeared less augmented following IV HSD infusion, but the differences were not statistically significant between the two groups (Figure 1B). It appeared that the greater augmentation in CO in the IO group was associated with an animal infused over 4 min. If this animal was eliminated

from the analyses, IO and IV infusion of HSD would have a more similar effect on CO. This pig, however, was retained in the analyses for completeness and because it did not affect the overall data interpretation.

Plasma volume in euvolemic pigs was expanded over 20% with both IO and IV infusion of HSD, as determined by Evan's Blue dye dilution (Figure 1C). Changes in hematocrit and plasma protein concentrations (Table 1) following HSD infusion also confirmed a similar expansion of plasma volume in these animals. Plasma volume expansion by either route of HSD administration was also independent of the 2-6 min infusion time.

Both IO and IV infusion of HSD resulted in a rapid rise in plasma dextran and Na concentrations 1 to 2 min following infusion (Fig. 2, Table 2). Although Na concentrations were significantly higher ($p<0.05$) at the end of the 2 h post-infusion period in comparison with baseline concentrations, the differences were not considered of clinical significance (Table 2). In contrast to Na, plasma dextran concentrations dropped more slowly during the post-infusion period and no significant differences were observed in dextran concentrations following either route of administration, suggesting no effect of infusion route on either dextran entry or the early phases of vascular clearance of dextran (Fig. 2). Peak Na and dextran concentrations also appeared to be independent of the varying infusion times encountered in this study, i.e., peak concentrations of Na or dextran occurred 1-2 min after the end of infusion. In addition, the method of infusion did not significantly affect plasma K^+ concentrations, although Cl^- rose immediately after infusion and then slowly returned towards pre-infusion levels (Table 2).

Total vascular dextran levels were calculated from plasma concentrations and plasma volume estimates to further evaluate delivery of dextran into the circulation. Estimated vascular dextran peaked at the end of the infusion period or at 1 min thereafter. Although estimated peak total vascular dextran tended to be higher in the IV than IO group, the differences were not statistically significant. It should be noted that the amount of dextran infused in the IO group (7.66 ± 0.50 g) was not significantly different from the amount infused in the IV group (7.14 ± 0.66 g). In both groups the data suggest that the total dose of dextran was accounted for in the vascular space and decreased about 25% after 2 h in both groups (data not shown). Thus, both

groups received similar amounts of dextran and the data obtained were again independent of infusion times.

Pathological Evaluation

As shown in Table 3, an equal number of pigs in each group had a minimal degree of acute to subacute pulmonary inflammation. Evidence for pulmonary thrombi or emboli was observed in both groups of pigs. When present, these emboli were small (<30 μ, diameter) and did not appear to occlude the vessels in which they were found, nor were they associated with lesions in the pulmonary vessels or parenchyma. In no case did the emboli consist of bone marrow components. Examination of the sternum revealed evidence of hemorrhage in 5/6 pigs infused IO with compared with 2/6 pigs infused IV (Table 3). Washout of sternal cellular marrow elements was observed in 1 pig in each group.

Discussion

The data from the present study indicate that IO infusion of HSD resulted in rapid vascular entry of Na and dextran, plasma volume expansion and augmentation of CO; i.e., all measures of sternal IO infusion were as efficacious as IV infusion. Using covariate analysis, these results were found to be independent of the 2 to 6 min infusion times required for IO administration of HSD into these pigs. Previous studies using IO infusion of various drugs have reported rapid distribution of the infused substance throughout the general circulation (12,20-22). Early studies by Tocantis, et al. (12) showed that a dye solution infused in the sternum leaves the marrow and enters the right heart very quickly. The vascular Na and dextran data from the present study are in agreement with these observations since plasma Na and dextran concentrations peaked by the end of infusion or within a minute thereafter. In addition, calculation of the estimated vascular dextran support complete delivery into the vasculature of the dextran infused IO.

In their studies of IO infusion of Ringer's lactate for the treatment of hypovolemia in dogs, Hodge, et al. (23) suggested that due to limitations in flow and fluid volumes

required, sufficient flow rates may not be attained for definitive treatment of hemorrhagic shock. Thus, the reduced volume requirements for effective resuscitation with HSD (18,24,25) make it a potential useful fluid for IO infusion. This is further supported by the observation that the infusion times in the present study are low and within the limits of infusion times employed for IV HSD administration (18,25). Recently, Chevez-Negrete, et al. (26,27) demonstrated that the adult sternum can be successfully used as a site for emergency resuscitation with 250 ml of HSD. Emergency room treatment of patients hypotensive from GI bleeding were treated more effectively with IO infusion of HSD than with IV infusion of crystalloids and blood (27). A third group treated with HSD IV, has a similar outcome to those infused IO.

The use of IO infusion methods has been limited by concerns of adverse reactions. Although a number of adverse reactions have been reported following IO infusion into both the tibia and the sternum (1,28), the complication rate of IO infusion appears no greater than that of IV infusion; the consequences of IO complications, however, can be greater. In particular, the effects of localized infection are often significantly more severe in bone than in vein and surrounding soft tissues (1,5,6). Fortunately, osteomyelitis is relatively rare after IO infusion, (1,5) suggesting that aseptic techniques are practical and effective. In addition, extravasation of infused fluids into the soft tissue over the sternum or into the pleural space are relatively rare, but reported complications (5). In the present study, we employed a new sternum needle designed to minimize both back flow along the needle shaft and to prevent puncture of the inner cortical bone (13).

As mentioned, the hydraulic resistance of red marrow is high, requiring greater infusion pressures than those generated by standard IV gravity drip or IV pressure bag (300 mm Hg) (8). In the present study, we used syringe delivery (1-2 atm pressure) to infuse 4 ml/kg HSD. Such pressurized delivery of fluids into the sternum is potentially dangerous because if the IO needle becomes dislodged or is not tightly imbedded in the bone, then soft tissue extravasation can occur. The needle used in the present study has a bulbous threaded head which lies entirely in the marrow. A wide, circular base and spring are designed to pull up on the bulbous head, seal the puncture hole, and stabilize the needle (13,15). In the

present study, sternal infusion of 4 ml/kg HSD did not cause clinically significant pulmonary bone or fat emboli, while marrow examinations showed only a small focal hemorrhage as the predominant effect of a single IO infusion of HSD, in agreement with our previous observations (29). In addition the nature of the device prevents complications such as sternal perforation or mediastinitus that have been previously associated with sternal IO infusion (1). Thus, extravasation of fluid into the skin over the sternum was not an observed complication in this study. However, the effects of multiple IO infusions with hypertonic infusions remain to be determined.

In conclusion, the present study indicates that IO infusion of HSD results in rapid delivery of dextran to the vasculature and expansion of plasma volume as effectively as IV infusion. In addition, the IO route did not appear to alter early phases of plasma dextran clearance and did not induce significant pathology to the sternum or lung. Thus, IO infusion of HSD may be a viable alternative for resuscitation from hypovolemia under conditions where access to peripheral vessels is compromised.

Acknowledgement

The authors thank Mr. Donald L. Calkins for preparation of the manuscript and the assistance of the Operating Room Staff of the Division of Military Trauma Research.

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Table 1

IO vs. IV Infusion of HSD on Plasma Protein Concentrations and Hematocrit[1]

	Protein (g/dl)		Hematocrit (%)	
	IO	IV	IO	IV
BL	5.62±0.23	5.34±0.22	26.0±1.3	27.4±1.2
0	4.65±0.14	4.59±0.13	20.0±1.0	21.9±1.8
1	4.58±0.19	4.57±0.15	20.8±1.2	21.4±0.8
2	4.63±0.19	4.68±0.16	21.6±1.3	20.5±0.7
4	4.80±0.20	4.53±0.17	21.8±1.3	22.5±0.9
6	4.75±0.22	4.48±0.23	22.1±1.5	22.8±1.2
10	4.92±0.17	4.62±0.15	22.0±1.5	23.0±1.1
15	4.56±0.26	4.73±0.12	21.5±1.7	22.7±1.2
30	4.85±0.25	4.65±0.14	22.7±1.6	23.3±1.2
45	4.75±0.27	4.60±0.14	22.8±1.7	23.8±1.1
60	4.87±0.25	4.58±0.08	22.9±1.9	24.4±1.3
90	4.95±0.26	4.67±0.14	23.6±2.1	26.0±1.3
120	5.00±0.24	4.64±0.12	26.6±1.6	25.4±1.6

[1]Data expressed as mean ±S.E. n=6 at each time point except n=5 at 15 min

[2]BL-Baseline values

[3]0 min denotes end of infusion period.

Table 2

IO vs. IV Infusion of HSD on Plasma Electrolytes[1]

Time (min)	Na (mEq/l)		K (mEq/l)		Cl (mEq/l)	
	IO	IV	IO	IV	IO	IV
BL[2]	144±1	142±2	4.7±0.1	4.4±0.1	106±2	105±1
O[3]	169±3	165±6	4.3±0.3	4.0±0.2	136±6	129±6
1	161±3	158±2	4.2±0.3	3.8±0.1	126±2	123±1
2	160±2	158±2	4.2±0.3	3.8±0.1	123±3	121±1
4	158±2	155±2	4.0±0.2	3.6±0.1	122±4	120±2
6	156±2	154±2	4.1±0.2	3.7±0.1	120±4	118±2
10	154±1	152±1	4.2±0.2	3.7±0.1	118±2	117±2
15	154±1	153±1	4.1±0.2	3.8±0.2	119±2	119±1
30	152±1	151±1	4.4±0.2	4.0±0.1	117±4	114±2
45	152±1	150±1	4.4±0.2	4.0±0.1	117±3	113±1
60	152±1	150±2	4.5±0.2	4.2±0.1	116±3	113±2
90	151±1	149±2	4.5±0.1	4.2±0.1	115±2	111±2
120	151±1	149±1	4.4±0.2	4.3±0.1	115±3	110±2

[1]Data expressed as mean ±S.E.; n=6 at each time point except n=3 at 15 min

[2]BL Baseline values

[3]O min denotes end of infusion period.

For Na, all times after infusion significantly different ($p<0.05$) from BL.

Table 3

Histological Observations Following IO or IV Infusion of HSD in Pigs

Treatment	Animal#	Lung Inflammation[1]	Sternum Thrombosis or Embolism[2]	Hemorrhage[1]	Washout[1,3]
Intraosseous	1	0	1/8	2	0
	2	1	2/6	3	0
	3	1	0	2	1
	4	1	0	0	0
	5	0	0	1	0
	6	0	0	2	0
Intravenous	1	0	0	3	0
	2	0	1/6	0	0
	3	1	2/5	0	1
	4	1	0	2	0
	5	1	1/6	0	0
	6	0	2/6	0	0

[1]Data expressed as severity grade where 0= no lesion; 1= minimal; 2= mild; 3= moderate; 4= marked; 5= severe

[2]Data represent number of sections with thrombi or emboli out of the number of sections examined. At least 5 sections were examined for each animal.

[3]Washout denotes washout of cellular marrow elements.

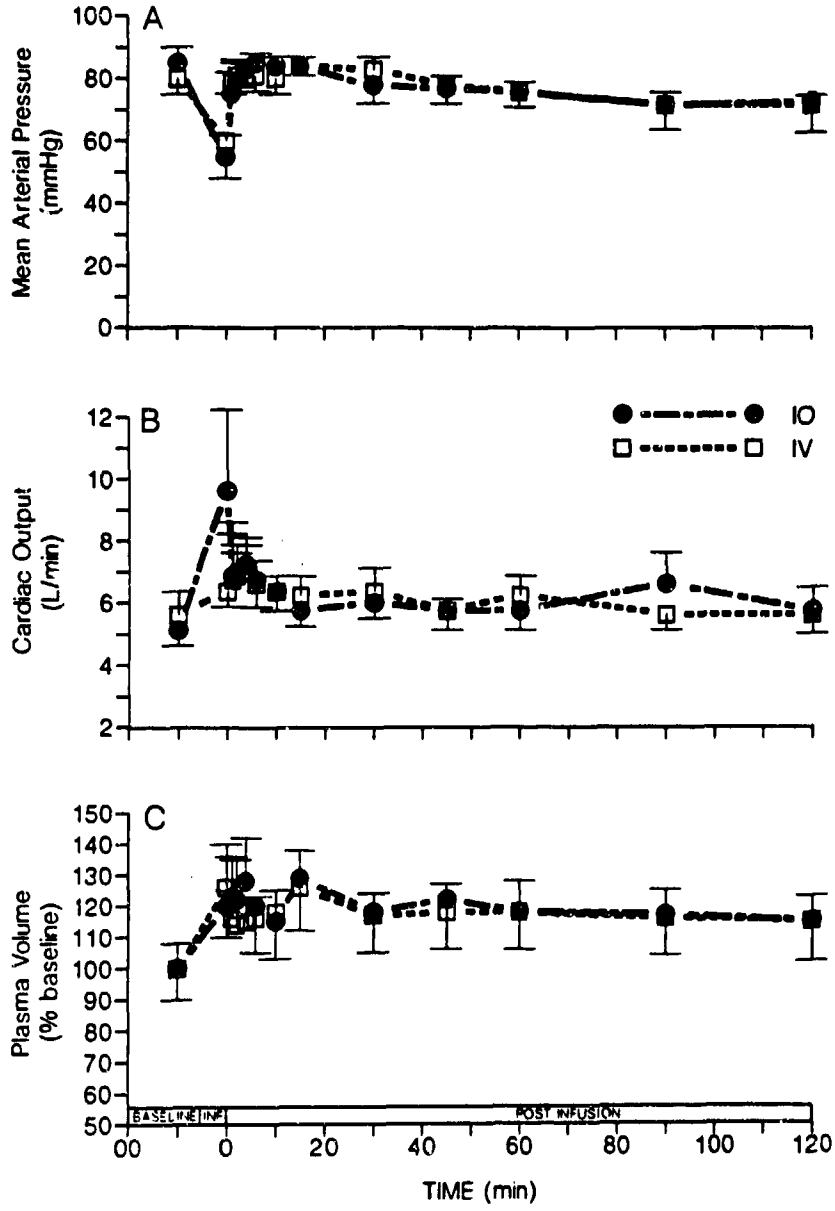

Fig 1. Effects of IO and IV infusion of HSD on A) mean arterial pressure, B) cardiac output, C) plasma volume expansion. Data represent mean ±S.E. of 6 matched experiments.

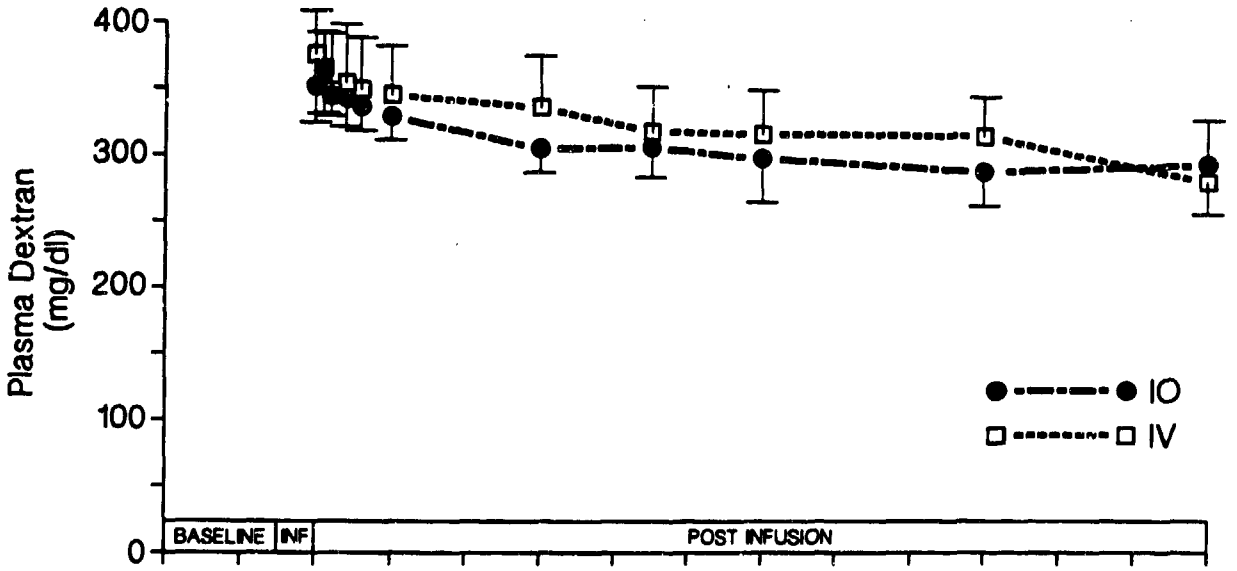

Fig 2. Plasma dextran concentrations following IO or IV infusion of 4 ml/kg HSD. Data represent mean ±S.E. of 6 matched experiments.

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